

Serial Number: 09/645,705

Filing Date: August 24, 2000

Title: SYNTHETIC NUCLEIC ACID MOLECULE COMPOSITIONS AND METHODS OF PREPARATION

Remarks

Claims 1, 18, 47, 67, 74, 78, 90, and 93-96 are amended, and claims 6, 83-85 and 91 are canceled. Claims 1, 3-5, 9, 11-12, 15, 18, 20-21, 24-39, 41-45, 47, 60, 64, 67, 69-71, 74, 76-78, 80-82, 86-88, 90, and 92-96 are pending.

In the Decision mailed September 3, 2008, the Board of Patent Appeals and Interferences (hereinafter the BPAI) reversed the rejection of claims 1, 3-6, 9, 11-12, 15, 20-21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78, 80-82, 85-88, and 90-96 under 35 U.S.C. § 112, second paragraph, and claims 1, 3-6, 9, 11-12, 15, 20-21, 24-33, 35-39, 41-45, 60, 67, 69, 70, 81, 86, 88, and 90-95 under 35 U.S.C. § 112, first paragraph, as not being enabled.

The BPAI affirmed the rejection of claims 1, 3-6, 9, 11-12, 15, 20-21, 24-39, 41-45, 60, 67, 69-70, 81, 86, and 91-95 under 35 U.S.C. § 103(a) over Sherf et al. (U.S. Patent No. 5,670,356) in view of Zolotukhin et al. (U.S. Patent No. 5,874,304), Donnelly et al. (WO 97/47358), Pan et al. (Nucl. Acids Res., 27:1094 (1999)), Cornelissen et al. (U.S. Patent No. 5,952,547), and Hey et al. (U.S. Patent No. 6,169,232); the rejection of claims 18, 47, 71, 74, 76-78, 80, 82-85, 87-88, and 96 under 35 U.S.C. § 103(a) over Sherf et al., in view of Zolotukhin et al., Donnelly et al., Pan et al., Cornelissen et al., and Hey et al., and further in view of Wood et al. (WO 99/14336); and the rejection of claims 91, 93 and 94 under the judicially created doctrine of obviousness-type doubling patenting over claims 1-50 and 58-60 of Serial No. 10/314,827.

The following remarks address the rejections that were affirmed in the Decision, as they may be applied to the amended claims.

The 35 U.S.C. § 103 rejections

In the Decision dated September 3, 2008, the BPAI asserts that the obviousness issue is would it have been obvious to an ordinary artisan to prepare synthetic nucleic acids which are optimized for expression using the teachings of Sherf et al., Zolotukhin et al., Donnelly et al., Pan et al., Cornelissen et al., and Hey et al., or it would have been obvious to an ordinary artisan to prepare synthetic nucleic acids which hybridize to the SEQ ID numbers listed in claim 18 using the teachings of Sherf et al., Zolotukhin et al., Donnelly et al., Pan et al., Cornelissen et al.,

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Hey et al., and Wood et al. KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727 (2007), is cited in support of the § 103 rejections.

First, one of skill in the art could not prepare synthetic nucleic acids which hybridize to the SEQ ID numbers recited in claim 18 without preparing the recited SEQ ID numbers.

Second, Applicant does not dispute that generally an artisan in view of the cited references would likely prepare synthetic nucleic acids which are optimized in some manner. However, why does each reference “optimize” a gene in a different way? That is because the purpose for the underlying changes must be different. That is, the cited documents disclose specific changes in specific genes for specific purposes. And while not explicit, there must have been a reason certain alterations were made and others were not. In this regard, the Examiner is requested to consider that each later dated document does not alter a gene with the cumulative alterations in documents with earlier dates of availability. Moreover, one of skill in the art would not likely incorporate all of the changes, as some changes must have a higher priority than others.

Further, there are contradictory teachings in the cited documents. For instance, Sherf et al. teach limited and specific changes to a gene while Zolotuhkin et al. teach some global changes (codon optimization) as well as more limited changes (inserting an intron or Kozak sequence), and some of the cited documents disclose eliminating splice sites to eliminate introns, while others disclose adding introns.

If, in fact, the more changes that are made to a sequence, the higher the chances are that a detrimental sequence will be introduced, one of skill in the art would follow the teachings of Sherf et al. or Cornelissen et al. which teach limited and targeted changes to address the problem addressed by Zolotuhkin et al., Donnelly et al., Pan et al., and Hey et al. Thus, by introducing limited changes, one of skill in the art creates fewer potential detrimental sequences.

In addition, it is likely relatively straightforward to remove a functional ATTTA sequence, splice site, restriction enzyme site, poly(A) signal, or remove TA and CG doublets, blocks of G or C residues of more than about 4 residues, peroxisomal targeting sequence, internal palindromic sequence, or glycosylation sites (sites disclosed for removal in Sherf et al., Cornelissen et al., Donnelly et al., Pan et al., and Hey et al.). In particular, perhaps only a single

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nucleotide replacement in a codon which forms part of a ATTTA sequence, intron splice site, restriction enzyme site, poly(A) signal, TA and CG doublet, block of G or C residues, peroxisomal targeting sequence, internal palindromic sequence, or glycosylation site without reference to adjacent sequences, may accomplish the removal of those undesired sequences. Moreover, sequences such as poly(A) sites, splice sites, and prokaryotic promoter sequences are fairly conserved.

In contrast, to remove a plurality of transcription factor binding sites (TFBS), optionally in conjunction with other classes of sequences, by replacing codons, those modifications are selected in context, i.e., with reference to how those modifications impact adjacent sequences.

Note that only a few TFBSs were removed from a wild type firefly luciferase sequence in the Sherf et al. patent, even though the Sherf et al. patent discloses that the luciferase gene sequences were scanned using a database of consensus TFBSs and that "[m]any sites which could potentially interact with common factors were removed. In some cases...less common potential regulating sites were also removed" (column 9, lines 1-4). Nevertheless, only 8 TFBS were modified (see Table 2 in Sherf et al.). And clearly not all TFBS that could potentially interact with TF were removed as the product of the disclosed improvements, *luc+*, had over 150 potential mammalian TFBSs (see the Wood Declaration filed on June 19, 2006), and other sites disclosed in Faisst and Meyer (Nucl. Acids Res., 20:3 (1992); of record), which was employed in Sherf et al. (see column 8, line 67), were likely still present in the wild-type sequence.

Given that of the 20 sites modified in Sherf et al. (see Table 2), 7 did not include codon usage improvement and 14 did not include TFBS alterations, i.e., codon optimization and TFBS alteration were independent, one of skill in the art would not reasonably expect that mammalian codon optimization and subsequent codon replacements would introduce mammalian TFBSs, particularly given the complexity of the sequence for many vertebrate TFBSs (see the table in Faisst and Meyer).

A reference teaches away from a claimed invention when it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994). Sherf et al. disclose that "the improved reporter activity is due to the inactivation of the peroxisomal targeting

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sequence and not to structural nuances of the modifications. Other modifications of the luciferases revealed that eliminating a palindrome sequence...also yielded greater expression" (column 13, lines 25-30). Thus, apparently modifications other than inactivation of the peroxisomal targeting sequence and elimination of palindromic sequences had little if any effect on reporter expression. Therefore, Sherf et al. teach away from modifications that include TFBS to improve reporter activity.

The issue in KSR v. Teleflex was whether mounting a modular sensor on a fixed pivot point of a pedal was a design step within the grasp of a person of ordinary skill in the art, in view of two cited documents. The Court noted that following the principles underlying case law with regard to obviousness "may be more difficult in other cases than it is here because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for improvement". Id., at 1396. The Court held that the claim at issue was obvious in view of the combination of the two cited documents.

In the present application, the claims were alleged to be obvious in view of a combination of six or seven documents. Moreover, in contrast to the claimed invention at issue in KSR v. Teleflex (a vehicle control pedal apparatus), the presently claimed subject matter does not involve the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art. In particular, in the Decision, the BPAI asserts that the evidence of record demonstrates that Applicant's combination is a predictable application of the prior art methods to remove unwanted sequences which interfere with expression.

Applicant's invention is not the simple substitution of one of the types of sites disclosed in, for example, Pan et al. for alteration of the *msh-1* gene, with the TFBS disclosed in Sherf et al. for alteration of the *luc* gene, or the mere application of identifying undesirable sites in a nucleic acid sequence for removal. There is nothing in the cited art that discloses the large number of mammalian TFBS that are present in a mammalian codon optimized reporter protein encoding sequence. Because higher usage codons are those employed more frequently in a particular organism and nucleic acid sequences likely evolved to not include spurious TFBS but to include generally higher usage codons, it was unexpected that introducing mammalian codons,

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or replacing mammalian high usage codons with other mammalian codons, introduced mammalian TFBS.

With regard to obvious-to-try, the Court in KSR v. Teleflex stated that where there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a combination that was obvious-to-try might show that the combination was obvious. Id., at 1397 (emphasis added).

It is Applicant's position that the documents cited against the claims solved the problem of gene optimization for each particular gene in a particular way for a particular purpose. And even if, assuming for the sake of argument, there was a need to provide other types of optimized genes, the combination of the cited documents does not provide a finite number of predictable solutions to prepare an improved gene. Clearly, the cited documents provide no single direction on how to "optimize" a gene nor the extent of that optimization, e.g., so as to result in a synthetic nucleic acid with at least 3-fold fewer of a combination of mammalian TFBS and optionally intron splice sites, poly(A) addition sites or prokaryotic 5' noncoding regulatory sequences relative to those in a wild-type nucleic acid sequence.

Accordingly, withdrawal of the § 103 rejections is respectfully requested.

The Nonstatutory Obviousness-Type Double Patenting Rejection

Claims 91, 93 and 94 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-50 and 58-60 of copending application Serial No. 10/314,827. Applicant notes that neither the present application nor the '827 application has issued. Therefore, a terminal disclaimer is not required in these matters until issuance of one of them. If a terminal disclaimer is required for either application, it can be requested by the Examiner before issuance.

Request For Telephone Interview

In an effort to advance prosecution, Applicant respectfully requests that, when the Examiner takes this application up for review, the Examiner call Applicant's attorney to set up a time for a telephone interview.

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CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

KEITH V. WOOD et al.,

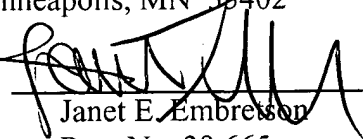
By their Representatives,

SCHWEGMAN, LUNDBERG, & WOESSNER, P.A.
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Date

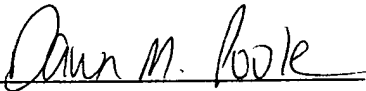
November 3, 2008

By


Janet E. Embresson
Reg. No. 39,665

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